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# Tetanus

## The Use of Human Hyperimmune Globulin in Treatment

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• Twenty patients with tetanus were treated with human hyperimmune globulin. The mortality rate in the series was 30 per cent. No complications due to the use of this antitoxin were observed.

ALTHOUGH TETANUS is a relatively uncommon disease, the long illness and high mortality associated with it increase its relative importance as a health problem. This is particularly true when one considers the numerous complications associated with both prophylaxis and therapy of this disease. The purpose of this report is to describe our experiences in treating a series of 20 patients with tetanus with relatively low doses of human hyperimmune globulin, thus completely avoiding animal serum reactions, which are serious and at times fatal complications of therapy in this disease.

The patients studied were admitted to the Communicable Disease Service of the Los Angeles County General Hospital between January 1, 1961, and October 5, 1962, for the treatment of definite clinical tetanus. The only patients excluded from the series were those receiving animal antitoxin before entry. None of the patients in this series had received tetanus toxoid at any previous time.

A single dose of 3,000 to 6,000 units of hyperimmune human globulin* was administered on admission to this hospital or as soon as the diagnosis was established. In general the larger doses were given to patients with either a rapidly progressing illness or a short incubation period. The hyperimmune human globulin is prepared from the sera of actively immunized humans by the Cohn cold ethanol fractionation procedure. It consists of 165± 15 mgm per ml of 100 per cent pure gamma globulin, 90 per cent of which is tetanus immune globulin. This antitoxin is prepared in the same manner as that supplied by the Red Cross, which has been amply demonstrated to be free of risk of transmitting viral hepatitis.[13]

The remainder of the clinical management followed established principles and involved special nurses, tracheostomy,[3,12] incision and drainage or local excision of the primary site when identified, penicillin and broad spectrum antibiotic therapy, and meprobamate†[6] given intramuscularly and supplemented in most cases by various other agents for sedation and control of muscular spasms.

*Hyper-tet® supplied by Dr. Walter E. Ward, Cutter Laboratories, Berkeley.

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†Supplied as "Miltown® Intramuscular" by Wallace Laboratories, Cranbury, New Jersey.

TABLE 1.—*Data on 20 Patients with Tetanus Treated with Human Hyperimmune Globulin*

| Patient No. | Age (Years) | Weight (Kilograms) | Units Human Tetanus Antitoxin | Units Per Kg of Weight | Duration of Antispasmodic Therapy (Days) | Outcome |
|---|---|---|---|---|---|---|
| 1 | 8 | 30 | 3,000 | 100 | 18 | Living |
| 2 | 7 | 20 | 6,000 | 300 | 16 | Living |
| 3 | 63 | 82 | 3,000 | 37 | 18 | Living |
| 4 | 71 | 64 | 4,500 | 70 | 9 | Died |
| 5 | 84 | 55 | 3,000 | 55 | 8 | Living |
| 6 | 3 | 17 | 3,000 | 177 | 16 | Living |
| 7 | 37 | 45 | 3,000 | 67 | 7 | Living |
| 8 | 47 | 67 | 3,000 | 45 | 13 | Living |
| 9 | 60 | 70 | 3,000 | 43 | 2 | Died |
| 10 | 4 | 16 | 4,500 | 281 | 14 | Living |
| 11 | 70 | 68 | 3,000 | 44 | 7 | Died |
| 12 | 49 | 91 | 4,500 | 50 | 5 | Died |
| 13 | 71 | 105 | 3,000 | 29 | 11 | Living |
| 14 | 46 | 85 | 3,000 | 35 | 2 | Died |
| 15 | 65 | 66 | 4,500 | 68 | 13 | Living |
| 16 | 76 | 68 | 3,000 | 44 | 2 | Died |
| 17 | 23 | 61 | 3,000 | 49 | 20 | Living |
| 18 | 5 | 15 | 3,000 | 200 | 8 | Living |
| 19 | 4 | 15 | 3,000 | 200 | 8 | Living |
| 20 | 47 | 54 | 3,000 | 56 | 13 | Living |

TABLE 2.—*Cause of Death in Six Cases of Patients with Tetanus Treated with Human Antitoxin*

| Patient No.* | Age | Cause of Death |
|---|---|---|
| 4 | 71 | Myocardial infarction, pneumonia. (No autopsy.) |
| 9 | 60 | Acute and old myocardial infarction. (Coroner's autopsy.) |
| 11 | 70 | Pneumonia, thrombophlebitis, recent cerebral artery occlusion. (No autopsy.) |
| 12 | 49 | Pneumonia, probably myocardial infarction. (No autopsy.) |
| 14 | 46 | Aspiration of blood secondary to laceration of tongue. (Coroner's autopsy.) |
| 16 | 76 | Acute and old myocardial infarction. (Coroner's autopsy.) |

*Refers to Table 1.

## RESULTS

In Table 1 the patients studied are listed with the amounts of antitetanus globulin given, the duration of continuous antispasmodic therapy as an indication of the severity of the disease, and the final outcome. There were six deaths in this group of twenty patients giving a total mortality rate of 30 per cent. The cause of death in three cases was confirmed by autopsy, and in the remainder the clinical cause of death is described (Table 2).

In no patient was there evidence of any kind of hypersensitivity reaction to the antitoxin either immediately following injection or during their hospital stay. There was no instance of unexplained fever, skin rash, arthritis, myocarditis or neurological involvement in any patient.

All of the six patients who died were over 45 years of age.

Two of the six deaths were due to advanced coronary atherosclerosis with proven fresh myocardial infarction. In two others acute myocardial infarction was the clinical cause of death but autopsy was not done. One patient had clinical evidence of pneumonia and a recent cerebral artery occlusion. One patient died suddenly after aspirating blood from a laceration of his tongue. The aspiration was confirmed by autopsy. None of the deaths appeared to be related to any possible adverse reaction to the antitoxin.

## DISCUSSION

The complications of therapy involving parenteral administration of animal serum are well known. These include potentially fatal anaphylactic reaction, "accelerated" serum sickness, classical serum sickness, various neurological complications such as demyelinating encephalomyelitis, the Guillain-Barre syndrome and polyneuritis, and sensitization of the patient, which increases the risk of an adverse reaction on any subsequent administration of animal serum. It is estimated that the incidence of serum sickness following a single prophylactic injection of 1,500 to 3,000 units of equine tetanus antitoxin is 30 per cent.[5] This may be reduced to 1.6 to 6 per cent[5,8,10] by the "de-speciated" horse serum now in common use. This incidence is, however, greatly increased with administration of larger volumes of equine or bovine serum and may be well above 50 per cent with the doses of 60,000 to 300,000 units of antitoxin which have been previously recommended for the therapy of tetanus.

Heterologous tetanus antitoxin has other characteristics limiting its effectiveness. It has been shown that equine antitoxin administered to a sensitive person gives unpredictable levels of circulating antitoxin and may be completely destroyed in four to nine days.[4] Smolens and coworkers[11] determined the half life of equine tetanus antitoxin to be only seven to fourteen days in non-sensitive persons. Skudder and coworkers[10] demonstrated that 55 per cent of persons were sensitive to equine serum as determined by reaction to an intradermal test. Approximately two-thirds of these persons were also sensitive to bovine serum. Furthermore, attempts to predetermine sensitive individuals by skin and conjunctival tests are frequently inaccurate and persons with positive reaction to such tests may require tedious "desensitization" to the foreign serum only to have the serum rapidly destroyed.

The use of hyperimmune gamma globulin of human origin can completely circumvent these difficulties. Human tetanus antitoxin has not been associated with hypersensitivity phenomena of any kind when given intramusclarly. It provides prolonged and predictable serum levels of antitoxin. It has a half life of four weeks and shows appreciable serum levels up to 14 weeks.[11] It has been shown in humans[7] that human antitoxin will produce protective blood levels of antitoxin in much smaller doses than equine tetanus antitoxin. The amount of antitoxin recommended by Rubbo and Suri[7] for tetanus prophylaxis was five units per kilogram of body weight, which consistently produced serum levels greater than 0.05 units per milliliter and protective levels that persisted for more than three weeks. The dose we used was selected on the basis of previous experimental work which indicated that levels of 0.08 to 0.160 per milliliter of serum would be achieved with 1,500 units of human antitoxin.[11] We chose to administer 3,000 to 6,000 units to purposely provide blood levels well in excess of these values. In this series the dose range was from 29 units to 300 units per kilogram of body weight. No difference in effectiveness was noted at the extremes.

The mortality rate in this series was 30 per cent. This compares favorably with our previous experience and that of others using antitoxin of equine origin in large doses. It also is much better than the 60 per cent death rate reported for the entire nation from 1951 to 1954.[1] This improvement cannot be attributed to the use of human antitoxin alone, as there are many other important factors in the treatment of tetanus. It is, however, worth noting that the six deaths in this series were all due to primary causes other than tetanus itself, and that all occurred in the over 45 age group, which would suggest that the presence of the degenerative diseases of older age greatly influence the prognosis in this disease.

Meprobamate given intramuscularly was helpful when used as a muscle relaxant. It was used in all but the first two cases in this series. However, it was necessary in all but two instances (Cases 9 and 19) to supplement this agent with various combinations of phenobarbital, amobarbital, chlorpromazine, promethazine and methocarbamol (Robaxin®) for sedation and for control of severe spasms. The dosage of meprobamate was 400 mg intramuscularly every three to four hours in adults and 200 mg every four hours in small children. Meprobamate by mouth was ineffective as a muscle relaxant.

## CONCLUSIONS

Human tetanus antitoxin used in the therapy of tetanus provides sustained levels of circulating antitoxin with no risk of the multiple manifestations of foreign serum hypersensitivity. A dose of 3,000 to 6,000 units of human tetanus antitoxin produces levels well in excess of recommended therapeutic levels.[2] It is recommended that human tetanus antitoxin replace the widespread use of equine or bovine antitoxin in the therapy of tetanus.

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